The specification was amended to include references to SEQ ID NOs as requested by the Examiner.

Claims 33-39 are introduced to more completely claim the present invention. Support for claims new 33-38 may be found *inter alia* in the specification. For example, support for claim 29 may be found on page 18, lines 1-5; and on page 15, lines 25-28. Support for claim 33 may be found page 18, lines 7-12. Support for claim 34 may be found on page 13, line 22. Support for claims 35, 36 and 37 may be found on page 18, line 28 to page 20, line 26. Support for claims 38 and 39 may be found on page 18, lines 12-19. Support may also be found on page 16, lines 6-7; page 16, lines 25-32; and page 17, line 35 to page 18, line 19. These amendments raise no issue of new matter and applicants respectfully requests their entry and consideration.

Election/Restriction

The Examiner stated that applicants' election with traverse of Group III and the species muteins (claims 29-30) in Paper No. 5 is acknowledged. The Examiner did not find applicants' argument persuasive and stated that the inventions require different ingredients, process steps and endpoints and the species are distinct because their structures and modes of action are different inventions. The Examiner stated that the requirement is still deemed proper and is therefore made final.

The Examiner withdrew claims 1-28 and 31-32 from further consideration as being drawn to non-elected inventions.

Information Disclosure Statement

The Examiner stated that the IDS previously filed refers to documents contained in the parent application Serial No.

08/721,447, all of which are available to the examiner except the following one document; Benedict, C. R., et al. (1994) "Endothelial-Dependent Pro-coagulation and Anti-coagulation Mechanisms." Texas Heart Journal, 21:86-90. The Examiner requested another copy of the Benedict document, and apologizes for any inconvenience.

In reply, applicants attach hereto as **Exhibit A**, a copy of Benedict et al. as requested by the Examiner.

Drawings

The Examiner stated that this application has allegedly been filed with informal drawings which are acceptable for examination purposes only and that they have not been reviewed by a draftsperson at this time. The Examiner stated that when formal drawings are submitted, the draftsperson will perform a review. The examiner stated that formal drawings will be required when the application is allowed. The Examiner stated to direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

In reply, applicants attach hereto 21 sheets of formal drawings for review by the draftsperson (attached hereto as **Exhibit B**). Applicants point out that these sheets were submitted as "formal drawings" upon filing of the subject patent application, not as "informal drawings" as stated by the Examiner. The Examiner is referred to the transmittal paper which was filed with the application on April 1, 1998 which indicates that 26 sheets of FORMAL drawings were included. Therefore, applicants request that the draftsperson review the drawings at this time and issue a Notice of Draftspersons Patent Drawing Review.

Sequence Listing

The Examiner stated that this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821 (a)(1) and (a)(2). The Examiner stated, however, this application fails to comply with the requirements of 37 CFR §1.821 through §1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Application Containing Nucleotide And/Or Amino Acid Sequence Disclosures. The Examiner stated that applicants are required to identify all such nucleotide and amino acid sequences in the specification with SEQ.ID NOS., including those sequences disclosed on pages 20 and 21 of the instant specification. Applicants attach a copy of the Notice to Comply with the Sequence Rules hereto as **Exhibit C**.

In reply, applicants submit herewith a Sequence Listing attached hereto as **Exhibit D** in compliance with the requirements of 37 C.F.R. §1.824. In addition, applicants submit herewith a computer readable copy of the Sequence Listing on the enclosed computer diskette, which has the same content as the paper copy attached as **Exhibit D**. Applicants submit as **Exhibit E**, a Statement in accordance with 37 C.F.R. §1.821(f) certifying that the computer readable form containing the nucleic acid and/or amino acid sequences required by 37 C.F.R. §1.821(f) and submitted in connection with the above-identified application, has the same information which is submitted herewith as **Exhibit D** entitled "Sequence Listing". In addition, applicants have amended the specification to include references to SEQ ID NOS.

Thus, applicants maintain that the application now complies with the requirements of 37 C.F.R. §1.824 and request that the Examiner withdraw this objection.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 29-30 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that there appears to be insufficient evidence that applicants' reliance on the mouse model of cerebral ischemia and reperfusion would indicate that the claimed therapeutic modalities based upon the administration of mutants of Factor IXai would be effective to inhibit clotting but not significantly impair hemostasis, commensurate in scope with the claimed invention.

The Examiner stated that animal model studies have not correlated well with in vivo results in patients. The Examiner stated that since the therapeutic indices of biopharmaceutical drugs can be species-and model-dependent, it is not clear that reliance on the in vivo experimental mouse models accurately reflects the relative efficacy of the administration of mutants of Factor IXai in the claimed therapeutic strategy of inhibiting clotting but not significantly impair hemostasis.

The Examiner stated that pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known

or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d (PTO Bd. Pat App. & Inter. 1992).

The Examiner stated that there is insufficient direction or guidance provided to assist one skilled in the art in the selection of any "inactive recombinant muteins" that are effective for inhibiting clotting but do not significantly impair hemostasis nor is there sufficient evidence provided that all such muteins are effective for inhibiting clotting but do not significantly impair hemostasis. The Examiner stated that it would require undue experimentation to produce all such possible muteins without more explicit guidance from the disclosure. The Examiner stated that it would require undue experimentation to investigate all such muteins. The Examiner stated that the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of inhibiting clot formation in the subject which does not significantly interfere with hemostasis when said muteins, broadly encompassed by the claims, are added to the blood administered to a patient.

The Examiner stated that since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a mutein's amino acid sequence and still retain the ability to inhibit clotting but not significantly impair hemostasis, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the Examiner stated that the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted

structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Also, the Examiner stated, minor structural differences among structurally related compounds or compositions can result in substantially different biological or pharmacological activities.

The Examiner stated that minor structural differences among structurally related compounds or compositions, such as amino acid substitutions at one or more of the following amino acids, Ser365, Asp269, and His221 of Factor IXa, can result in substantially different biological or pharmacological activities affecting clot formation and hemostasis. The Examiner stated that given the lack of guidance concerning the nature of the modifications associated with muteins that the skilled artisan could use as a guide in making said muteins; it would require undue experimentation to practice the claimed invention.

The Examiner stated that the applicant has not enabled or provided sufficient guidance to those skilled generally on how to make and use all muteins that inhibit clotting but do not significantly impair hemostasis. The Examiner stated that reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The Examiner stated that it appears that undue experimentation would be required of one skilled in the art to practice all the claimed muteins that inhibit clotting but do not significantly impair hemostasis, commensurate in scope with the claimed invention using the teaching of the specification.

The Examiner stated that in view of the lack of predictability of the art to which the invention pertains, undue experimentation would be required to practice the claimed methods with a

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reasonable expectation of success, absent a specific and detailed description in applicants' specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting clotting but do not significantly impair hemostasis.

In reply, applicants respectfully traverse the rejection and maintain that claims 29 and 30 are fully enabled by the subject application and that one of skill in the art would be able to make and use the claimed invention without undue experimentation. Claim 29 has been amended and new claims 33-39 have been introduced to more completely claim the present invention.

The term "inactive recombinant mutein" has been further characterized in claim 29 as comprising (a) a proteolytically inactive recombinant mutein of Factor IX, or (b) a proteolytically inactive recombinant mutein of Factor IXa and wherein the recombinant mutein comprises a substitution, deletion or addition of one or more amino acids to wild-type Factor IX or Factor IXa resulting in reduced ability to convert Factor X to Factor Xa. These two types of muteins are extensively described in the specification and the amended claim 29 is fully enabled by the specification. Several possible embodiments of such muteins are exemplified in new dependent claims 33 to 39. The amendments to claim 29 and the new claims 33-39 are fully supported by the specification (see Remarks section above) and have been included to more completely and particularly point out the presently claimed invention.

The presently claimed invention is fully enabled by the original specification, in that one of skill in the art at the time of filing would have been able to carry out the claimed invention without undue experimentation. Murine models of human disease

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have been utilized in many areas of scientific work and have correlated directly to many human therapies. The Examiner is referred to the many references included in the specification itself at page 30, lines 15-21. Moreover, this application describes a reproducible mouse model of focal cerebral infarction which provides consistent results and which provides an improvement over previous mouse models of human disease.

Clearly, it is well settled that an applicant need not enable "all" possible embodiments of a claimed invention as a prerequisite to patentability. The Examiner indicates that "it would require undue experimentation to investigate all such muteins" and that applicants have failed to enable those skilled in the art to make and use "all muteins that inhibit clotting but do not significantly impair hemostasis." The M.P.E.P. indicates in section 2164.02 that "compliance with the enablement requirement of 35 U.S.C. §112, first paragraph does not turn on whether an example is disclosed." Furthermore, the M.P.E.P. states that "because only an enabling disclosure is required, applicant need not describe all actual embodiments." (Emphasis added.)

Applicants point out that working examples are provided in the subject specification and contend that the working examples presented along with the description would allow one skilled in the art to practice the claimed invention without undue experimentation. Applicants point out that the specification describes many examples of muteins which may be utilized in the claimed method. In addition, the specification describes other muteins which one of skill in the art would know how to make and use in the claimed method. See the subject specification, for example pages 15-25.

The Examiner has stated that "in the absence of *in vivo* clinical

data" pharmaceutical therapies are allegedly unpredictable. Applicants point out that the standards for obtaining FDA approval may require *in vivo* clinical trials, but this high standard is not required for a showing of patentability. (See *Scott v. Finney* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosethic device is more properly left to the [FDA].")
Applicant also points out the following:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed.Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

See M.P.E.P. §2164.01. Any experimentation which may be necessary to practice the claimed invention would not be undue experimentation. The present specification includes an extensively characterized mouse model of ICH which provides results which are indicative of success in other animals and humans. See Example 1 beginning on page 31 which provides specific technical aspects of a murine model of focal cerebral ischemia and reperfusion which permits reproducibility of measurements of hemostasis. There may need to be routine optimization of such parameters as dose and pharmaceutical carriers, etc., but this is not undue experimentation.

Table II in the specification summarizes results obtained with the improved mouse model. Specifically, when stroke outcomes were measured 24 hours following surgery, animals that had received Factor IXai had smaller infarct volumes, improved cerebral perfusion, less neurological deficits, and reduced mortality compared with controls which underwent the same surgery but which did not receive Factor IXai. (See Table II.) It was

also noted that the Factor IXai animals were free of apparent intracerebral hemorrhage. The murine model provided by the subject specification has been tested to show predictability and consistency in results. Thus, one of skill in the art would have been fully enabled to carry out the claimed method given the teachings of the present specification.

In view of the amendments and discussion, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 29 and 30 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that the instant claims are indefinite in that they only describe the compounds of interest by an arbitrary name, "inactive recombinant mutein". The Examiner stated that the applicant should particularly point out and distinctly claim what is meant by inactive recombinant mutein by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.).

The Examiner stated that the term "significantly interfere with hemostasis" in claim 29 is a relative term which renders the claim indefinite. The Examiner stated that the term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

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In reply, applicants respectfully traverse the rejection. Claims 29-39 are fully described by the specification and particularly point out and distinctly claim the presently claimed invention. The phrase "inactive recombinant mutein" has been characterized in claim 29 and this amendment raises no issue of new matter. Claims 33-39 have been introduced to more completely claim the presently claimed invention.

The term "significantly" is clearly defined in the specification and does not render the claims indefinite. The Examiner is directed to page 75, lines 14 to 25 wherein applicants state that a compound is useful which is "significantly protective (reduced cerebral infarction volume) without causing any excess in intracerebral hemorrhage." On page 58, lines 14-24, applicants point out that a compound is useful in the claimed method if it does not increase the risk of ICH. It is recognized by applicants that a combination of beneficial properties and a "relatively low downside risk of hemorrhagic transformation" are needed. The Examiner is also directed to page 56, line 25 to page 57, line 29. Therein, applicants recognize a "dynamic equilibrium" between ongoing thrombosis and ongoing fibrinolysis.

> In the current studies, treatment with Factor IXai reduces microvascular platelet and fibrin accumulation, improves postischemic cerebral blood flow, and reduces cerebral infarct volumes in the setting of stroke without increasing ICH.

See page 57, lines 4 to 8. In addition, there are numerous studies described throughout the Experimental Details section which recount the effect of administered compounds upon the subject as to thrombosis and fibrinolysis.

In view of the amendments and discussion, applicants respectfully

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request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 29-30 under 35 U.S.C. §102(b) as being anticipated by Insley et al. (US Patent 4,711,848).

The Examiner stated that Insley et al. teach the mutant form of alpha-1 antitrypsin (AT) having an arginine substituted for methionine at amino acid position 358 which caused the mutant to convert from an elastase inhibitor to that of a thrombin inhibitor. The Examiner stated that Insley et al. teach methods of making site specific mutants of AT and that altered forms of AT that could be clinically important for use in inhibiting blood clotting, as for example, in the treatment of disseminated intravascular coagulation, (entire article, especially column lines 30-40). The Examiner stated that the applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The Examiner stated that the claimed functional limitations of the method of inhibiting clot formation, so as to not significantly interfere with hemostasis, would be inherent properties of the referenced method using a mutated AT.

In reply, applicants traverse the rejection and point out that claim 29 has been amended to more particularly point out the claimed invention. This amendment obviates the rejection over Insley et al. because Insley et al. do not teach at all a recombinant mutein of either Factor IX or Factor IXa. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

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Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 29-30 under 35 U.S.C. § 102(b) as being anticipated by Moller et al. (CA 2,141, 642, in PTO-1449).

The Examiner stated that Moller et al. teach the use of a factor IXA mutein which does not show coagulation activity and does not significantly interfere with hemostasis as a method to treat ischemic events encompassed by the claimed methods (see entire document, including pages 1-2), applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced treatment of ischemic events associated with thrombotic disease using muteins (fragments) of factors IX and IXa.

In reply, applicants respectfully traverse the rejection and maintain that Moller et al. do not teach or anticipate the presently claimed invention. Claim 29 calls for inactive recombinant muteins. Muteins are mutated proteins. Applicants provide several examples of "proteolytically inactive recombinant muteins" of Factor IX or Factor IXa in the specification.

> The present invention provides for a proteolytically inactive recombinant mutein of Factor IX, which has substantially the same amino acid sequence as normal Factor IX but which has an amino acid substitution for one or more of His221, Asp269 or Ser365. In one embodiment, the mutein has a Ser365 to Ala substitution.
>
> The present invention also provides a proteolytically inactive recombinant mutein of Factor IXa which has substantially the same amino acid sequence as normal human Factor IXa but which has an amino acid substitution for one or more of His41, Asp89

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> or Ser185 in the heavy chain of Factor IXa. In one embodiment, the mutein has a Ser185 to Ala substitution.

See page 14, lines 18-29 of the specification.

Moller et al. merely teach fragments of Factor IX, not muteins of Factor IX. Furthermore, Moller et al. do not disclose the use of any fragments or muteins of of Factor IXa. For example, page 5 of Moller et al. merely recites "the EGF-domain of Factor IX..."; page 8 of Moller et al. recites "use of Factor IX fragments according to the invention...."; and page 17 recites injection of Factor IXa into rabbits. Therefore, applicants maintain that Moller et al. do not anticipate the claimed invention.

Applicants point out that claim 29 has been amended hereinabove and claims 33-39 were introduced to more completely claim the present invention. Moller et al. do not teach or anticipate any particular amino acid substitutions of Factor IX or Factor IXa.

Applicants maintain that Moller et al. do not anticipate the presently claimed invention and respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 29-30 under 35 U.S.C. § 103 as being unpatentable over Moller et al. (CA 2,141,642, in PTO-1449) in view of Brandstetter et al. (PNAS 92:9796-800, 1995) and Insley et al. (US Patent 4,711,848).

The Examiner stated that the claims are drawn to a method of inhibiting clot formation in a patient, which comprises adding an inactive recombinant mutein to inhibit clot formation but

which does not significantly interfere with hemostasis. The Examiner stated that claim 30 has no further limitation wherein the patient has experienced an ischemic event.

The Examiner stated that Moller et al. teach the use of fragments of factors IX and IXa, which do not show coagulation activity as a method to treat thrombotic diseases encompassed by the claimed methods (see entire document, including pages 1-2 and 20), but do not teach specific amino acid substitutions of Factor IXa.

The Examiner stated that Brandstetter et al. teach the spatial distribution of variants of Factor IXa that have been identified in clinical studies in hemophiliacs, and in particular teaches the catalytic residues SER 365 and HIS 221 that are in the active site of the serine protease (see entire document, especially page 9797, paragraph three). The Examiner stated that inhibitory recombinant muteins of factor IXa of said two residues were referred to in the instant specification.

The Examiner stated that Insley et al. teach as described above.

The Examiner stated that by Moller's teaching of treating thrombotic diseases, it would have been obvious to treat patients who have experienced an ischemic event encompassed by the claim 30 because it would have been expected that inhibition of the coagulation cascade and thrombosis as taught by Moller et al. would inhibit the vascular complications and thrombosis associated with an ischemic event. The Examiner stated that it was known at the time the invention was made that ischemia or deprivation of oxygen was due, in part, to coagulation or thrombosis and that the treatment of such conditions relied upon anti-coagulants. The Examiner stated that the dosage range and routes of administration (intravascular) were all known at the time the invention was made and would have depended upon the

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needs of the subject for a particular ischemic event as they read on "an amount of an inactive recombinant mutein...effective to inhibit clot formation in the subject but which does not significantly interfere with hemostasis...".

The Examiner stated, therefore, the ordinary artisan at the time the invention was made, would have been motivated to substitute the mutations in Factor IX found in hemophiliacs as taught by Brandstetter et al., for the inhibitory fragments of factors IX and IXa taught by Moller et al, said mutations being produced according to the method of making recombinant mutants of Factor IX as taught by Insley et al., in order to accomplish a successful method of inhibiting clot formation in a subject or a patient who has experienced an ischemic event using an inhibitory factor IXa that does not significantly interfere with hemostasis taught by Moller and encompassed by the instant claims.

The Examiner stated that from the teachings of the reference and of that known and practiced by the ordinary artisan, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

In reply, applicants traverse the rejection. Claim 29 has been amended to include further characterization of the recombinant mutein and claims 33-39 have been introduced to more completely claim the present invention. Moller et al., as discussed hereinabove, do not teach or suggest the present invention. Moller et al. merely disclose use of fragments of Factor IX. There is no disclosure of a mutein of Factor IX or of Factor IXa. There is no disclosure or suggestion or teaching of a proteolytically inactive mutein of Factor IX or Factor IXa. A "proteolytic fragment" as disclosed in Moller et al. does not

include muteins, that is mutated proteins.

Disclosure of a "fragment" of a protein does not and cannot teach or suggest a mutein. A fragment is merely a piece of the intact whole normal protein. A mutein is a mutated protein and has been altered by a substitution, deletion or addition amino acids. The specification provides many examples of such muteins, see pages 20-21. For example, the specification states

> [a]s used herein, "mutein form" of Factor IXa means a protein which differs from natural factor IXa by the presence of one or more amino acid additions, deletions, or substitutions which reduce or eliminate the ability of the protein to participate in the conversion of Factor X to Factor Xa.

Therefore, Moller et al. do not teach or suggest the presently claimed invention.

The disclosure of Brandstetter et al. combined with Moller et al. would not teach one of skill the claimed invention. Brandstetter et al.'s disclosure of x-ray structures of Factor IXa in hemophiliacs would suggest to one of ordinary skill that the structures disclosed would be harmful if administered to a human. The authors merely suggest the use of the structures as a framework for localizing the interation sites involved in Xase function. (See last sentence of article.) There is no disclosure or suggestion of the claimed methods when Moller et al. and Brandstetter et al. are combined.

Finally, applicants point out that there is <u>no motivation</u> to combine Moller et al., Brandsetter et al. and Insley et al. The Examiner is referred to applicants' discussion of Insley et al. hereinabove. Insley et al. do not teach or suggest the presently claimed invention when combined with Moller et al. and

Brandsetter et al. Insley et al. merely teach site specific mutagenesis of alpha-1-antitrypsin. This is an irrelevant protein with no relation to Factor IX or Factor IXa. Thus, there is clearly no motivation to combine Insley et al. with Moller et al. or Brandsetter et al.

Applicants request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee other than the $435.00 extension of time fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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